

66-

**This Page Is Inserted by IFW Operations
and is not a part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images,
please do not report the images to the
Image Problem Mailbox.



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 9/22		A1	(11) International Publication Number: WO 99/51209 (43) International Publication Date: 14 October 1999 (14.10.99)
<p>(21) International Application Number: PCT/US99/06987</p> <p>(22) International Filing Date: 31 March 1999 (31.03.99)</p> <p>(30) Priority Data: 09/053,491 2 April 1998 (02.04.98) US</p> <p>(71) Applicant: IMPAX PHARMACEUTICALS, INC. [US/US]; 30831 Huntwood Avenue, Hayward, CA 94544 (US).</p> <p>(72) Inventors: TING, Richard; 38 Woodranch Circle, Danville, CA 94506 (US). HSIAO, Charles; 2012 Westbrook Lane, Livermore, CA 94550 (US).</p> <p>(74) Agent: SUNG, Lawrence; Arter & Hadden, LLP, Suite 400K, 1801 K Street, N.W., Washington, DC 20006 (US).</p>		<p>(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>	

(54) Title: PRESS COATED, PULSATILE DRUG DELIVERY SYSTEM SUITABLE FOR ORAL ADMINISTRATION

(57) Abstract

A press coated, pulsatile drug delivery system suitable for oral administration having an immediate-release compartment, which contains a compressed blend of an active agent and one or more polymers, substantially enveloped by an extended-release compartment, which contains a compressed blend of the active agent and hydrophilic and hydrophobic polymers, can provide a substantially first order delivery of the active agent, interrupted by a timed, pulsed delivery of an increased amount of the active agent; and when the extended-release compartment is substantially enveloped by an optional instant-release compartment, can provide a dose sufficient to exceed the liver's metabolic capacity and to maintain therapeutic levels, preferably throughout a 24-hour period.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		

PRESS COATED, PULSATILE DRUG DELIVERY SYSTEM
SUITABLE FOR ORAL ADMINISTRATION

Field of the Invention

The present invention pertains to a drug delivery system suitable for oral administration that facilitates a pulsatile release of the active agent. A key aspect of the present invention is the discovery that a tablet with an immediate-release compartment, which contains a compressed blend of an active agent and one or more polymers, substantially enveloped by an extended-release compartment, which contains a compressed blend of the active agent and hydrophilic and hydrophobic polymers, can provide a substantially first order delivery of the active agent, interrupted by a timed, pulsed delivery of a preferably increased amount of the active agent. With respect to drugs subject to "first pass" clearance, sustained drug delivery can be achieved through the present invention via an optional instant-release compartment, which provides a dose sufficient to exceed the liver's metabolic capacity and to maintain therapeutic levels, preferably throughout a 24-hour period.

Background of the Invention

Drug efficacy generally depends upon the ability of the drug to reach its target in sufficient quantity to maintain therapeutic levels for the desired time period. The pulsatile release of an active agent is desirable when treating diseases that require drug delivery in a manner to maintain therapeutic levels notwithstanding circadian rhythms. Diseases that benefit from pulsatile drug delivery include angina, for example, which occurs with repeatable regularity at the end of the night and in the early morning hours while the patient is still asleep, and rheumatic diseases such as rheumatoid arthritis, the symptoms of which manifest during the night and into the beginning of the next day. With traditional extended-release dosage formulations, which exhibit first order release rates, the efficacy of the active agent diminishes at the end of the night and the

beginning of the next day. Therefore, a bolus or burst delivery of the active agent during this waning period can improve drug efficacy.

In addition, orally administered drugs must overcome several obstacles to reach their desired targets. Before orally administered drugs enter the general circulation of 5 the human body, they are absorbed into the capillaries and veins of the upper gastrointestinal tract and are transported by the portal vein to the liver. The pH and enzymatic activities found in gastrointestinal fluids may inactivate the drug or cause the drug to dissolve poorly. Following their absorption in the intestine, certain orally administered drugs can be subject to a "first pass" clearance by the liver and excreted 10 into bile or converted into pharmacologically inactive metabolites. Decreased bioavailability of orally administered drugs can be a consequence of this first pass effect.

Orally administered drugs subject to the first pass effect generally exhibit non-linear pharmacokinetics. Until the liver's metabolic capacity has been exceeded, the amount of such drugs in the bloodstream is significantly lower than the amount 15 administered. This metabolic elimination of the given dose results in reduced bioavailability. However, once the administered dose exceeds the liver's metabolic capacity, a significant increase in the drug concentration in the bloodstream may be obtained. The first pass phenomenon presents particular difficulties in the maintenance of therapeutic levels of an orally administered drug over an extended period such as 12 20 or 24 hours.

Drug delivery systems that have evolved with respect to orally administered drugs subject to the first pass effect include formulations capable of immediate drug release that are suitable for administration from 3-4 times daily, and formulations capable of immediate and sustained drug release that are suitable for once-daily 25 administration. The second type of formulation is preferred because patient compliance

with prescribed drug regimens involving once-daily administration is substantially higher than those involving multiple administrations. A sustained release formulation, however, may subject the patient to toxic drug levels over part of the dosing period and sub-therapeutic drug levels over other portions of the dosing period, if the drug release 5 does not occur at appropriate time intervals. The maintenance of therapeutic levels of an orally administered drug over an extended period thus depends upon a drug delivery system capable of providing an appropriate release pattern.

A valuable contribution to the art therefore would be the development of a drug delivery system in a single tablet formulation suitable for oral administration that 10 facilitates a substantially first order delivery of the active agent, interrupted by a timed, pulsed delivery of a preferably increased amount of the active agent, and where the active agent is subject to "first pass" clearance, can provide sustained drug delivery, preferably over a 24-hour period, by a dose sufficient to exceed the liver's metabolic capacity and to maintain therapeutic levels.

15

Summary of the Invention

Accordingly, an objective of the present invention is a single orally administrable tablet that can provide a substantially first order delivery of the active agent, interrupted by a timed, pulsed delivery of an increased amount of the active agent. A second objective of the present invention is a single orally administrable tablet that can 20 overcome the "first pass" effect by providing an instant-release dosage sufficient to exceed the liver's metabolic capacity, and then continue to maintain therapeutic drug levels, preferably over a 24-hour period. A further objective of the present invention is a method for preparing of a single orally administrable tablet that can provide a substantially first order delivery of the active agent, interrupted by a timed, pulsed 25 delivery of a preferably increased amount of the active agent.

In a preferred embodiment of the invention, these and other objectives can be accomplished through a drug delivery system suitable for oral administration with an immediate-release compartment, which contains a compressed blend of an active agent and one or more polymers, substantially enveloped by an extended-release compartment,

5 which contains a compressed blend of the active agent and hydrophilic and hydrophobic polymers, and substantially enveloped by an optional instant-release compartment, which provides a dose sufficient to exceed the liver's metabolic capacity and to maintain therapeutic levels, preferably throughout a 24-hour period.

In a preferred embodiment of the present invention, the active agent in the

10 extended-release compartment can diffuse out first, resulting in a first order release rate. As the active agent and soluble polymers in the extended-release compartment disintegrate, water will penetrate through the extended-release compartment and cause the immediate-release compartment to expand, creating a bursting effect that further disrupts any remaining integrity of the extended-release compartment. Where an

15 optional inert core (*i.e.*, a core containing one or more polymers without active agent) is present, its swelling in response to the water influx described above can also contribute to a bursting effect. The respective time periods for the dissolution of the active agent, and the bursting effect, can be regulated by varying the composition and relative amounts of the polymers in the compartments.

20 The extended-release compartment preferably comprises a combination of hydrophilic and hydrophobic polymers. In this embodiment, once administered, the hydrophilic polymer dissolves away to weaken the structure of the extended-release compartment, and the hydrophobic polymer retards the water penetration and helps to maintain the shape of the drug delivery system. The immediate-release compartment

25 preferably comprises a compressed blend of active agent and one or more polymers with

disintegration characteristics, which upon exposure to the aqueous medium, would burst to further break apart the already weakened extended-release compartment and provide preferably complete drug release. In another embodiment, the immediate-release drug compartment and the combination of hydrophilic and hydrophobic polymers in the 5 extended-release drug compartment can be modified so the second peak does not result in a burst. Instead, the second peak can be tailored to be completed in a desired time interval, for example, 30 minutes to 12 hours after release of active agent from the extended-release compartment.

In another embodiment, the extended-release compartment can be inert (*i.e.*, 10 containing a combination of hydrophilic and hydrophobic polymers without active agent), which may be preferable where delayed drug release is necessary or convenient. For example, if orally administered before bedtime, this drug delivery system could deliver its active agent while the patient is asleep to facilitate optimal therapeutic drug levels just prior to awakening.

15 In a preferred embodiment, the active agent is a drug, which may be a therapeutic drug or a prophylactic drug. In another preferred embodiment, the drug can be diltiazem, trapidil, urapidil, benziodarone, dipyridamole, isosorbide mononitrate, or lidoflazine. In yet another, the drug can be a non-steroidal antiinflammatory drug (NSAID) or a steroid antiinflammatory drugs, which includes diclofenac sodium, 20 ibuprofen, ketoprofen, diflunisal, piroxicam, motrin, and naproxen.

In still another preferred embodiment, the drug can be acetaminophen, aldosterone, alprenolol, amitryptyline, aspirin, beclomethasone, dipropionate, bromocriptine, butorphanol tartrate, chlormethiazole, chlorpheniramine, chlorpromazine HCl, cimetidine, codeine, cortisone, cyclobenzamine HCl, desmethylimipramine, 25 dextropropoxyphene, dihydroergotamine, diltiazem HCl, dobutamine HCl,

domperidone, dopamine HCl, doxepin HCl, epinephrine, ergoloid mesylates, ergotamine tartrate estradiol, ethinylestradiol, flunisolide, fluorouracil, flurazepam HCl, 5-fluoro-21-deoxyuridine, furosemide, glipizide, glyburide, glyceryl trinitrate, guanethidine sulfate, hydralazine HCl, imipramine HCl, indoramin, isoetharine HCl, isoethrine mesylate,

5 isoprenaline, isoproterenol sulfate, isosorbide dinitrate, levallorphan tartrate, levodopa, lidocaine HCl, lignocaine, lorcainide, meperidine HCl, 6-mercaptopurine, metaproterenol sulfate, methoxamine HCl, methylphenidate, methylpreonisolone, methyltestosterone mesylate, metoclopramide, metoprolol tartrate, morphine sulfate, nalbuphine HCl, naloxone HCl, neostigmine, nifedipine, nitrendipine, nitroglycerin,

10 norepinephrine bitartrate, norethindrone, nortriptylene HCl, oxprenolol, oxyphenbutazone, penicillamine, pentazocine HCl, pentazocine lactate, pentobarbital, petnidine, phenacetin, phentolamine HCl, phentolamine mesylate, phenylephrine HCl, phenylephrine bitartrate, phenytoin, pindolol, prazosin, prednisone, progesterone, propoxyphene HCl, propoxyphene napsylate, propranolol HCl, quinidine, reserpine,

15 ritodrine HCl, salicylamide, salbutamol, secobarbital, testosterone, terbutaline, timolol maleate, tolbutamide, or verapamil HCl.

In another preferred embodiment, the active agent can be isosorbide-5-mononitrate.

In a preferred embodiment, the active agent of the drug delivery can exhibit the following *in vitro* dissolution profile when measured in a type 2 dissolution apparatus (paddle) according to U.S. Pharmacopeia XXII at 37°C in deionized water at 75 rotations per minute:

(a) from about 0% to about 90% of said active agent is released between 1 hour and 16 hours of measurement in said apparatus; and

(b) from about 0% to about 100% of said active agent is released between 1.5 hours and 28 hours after measurement in said apparatus.

In another preferred embodiment, the active agent of the drug delivery system can exhibit the following *in vitro* dissolution profile when measured under the same 5 conditions described above:

(a) from about 10% to about 75% of said active agent is released between 1 hour and 5 hours of measurement in said apparatus; and
(b) no less than about 90% of said active agent is released after 6 hours of measurement in said apparatus.

10 In yet another preferred embodiment, the active agent of the drug delivery system exhibits the following *in vitro* dissolution profile when measured under the same conditions described above:

(a) from about 0% to about 50% of said active agent is released after 1 hour of measurement in said apparatus;
15 (b) from about 0% to about 90% of said active agent is released between 1 hour and 16 hours after measurement in said apparatus; and
(c) from about 0% to about 100% of said active agent is released between 1.5 hours and 28 hours after measurement in said apparatus.

In still another preferred embodiment, the active agent of the drug delivery 20 system exhibits the following *in vitro* dissolution profile when measured under the same conditions described above:

(a) from about 0% to about 35% of said active agent is released after 1 hour of measurement in said apparatus;
25 (b) from about 10% to about 90% of said active agent is released between 1 hour and 5 hours after measurement in said apparatus; and

(c) no less than 90% of said active agent is released after 6 hours

of measurement in said apparatus.

In a preferred embodiment, the active agent exhibiting these dissolution profiles

can be isosorbide-5-mononitrate.

5 In a preferred embodiment, the polymer of the drug delivery system can be alginic acid, carboxymethylcellulose calcium, carboxymethylcellulose sodium, colloidal silicon dioxide, croscarmellose sodium, crospovidone, guar gum, magnesium aluminum silicate, magnesium stearate, methylcellulose, microcrystalline cellulose, polacrilin potassium, powdered cellulose, pregelatinized starch, sodium alginate, sodium starch 10 glycolate, starch, ethylcellulose, gelatin, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polymethacrylates, povidone, shellac, or zein, of which colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, microcrystalline cellulose, and hydroxypropyl methylcellulose are further preferred.

In a preferred embodiment of the invention, the hydrophilic polymer can be

15 carboxymethylcellulose, guar gum, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose, or povidone, of which hydroxypropyl methylcellulose is further preferred.

In another embodiment, the hydrophobic polymer of the drug delivery system can be carbomer, carnauba wax, ethylcellulose, glyceryl palmitostearate, hydrogenated 20 castor oil, hydrogenated vegetable oil type 1, microcrystalline wax, polacrilin potassium, polymethacrylates, or stearic acid, of which hydrogenated vegetable oil type 1 is further preferred.

The present invention also accomplishes these and other objectives through a method for preparing a press coated, pulsatile drug delivery system suitable for oral 25 administration including the steps of combining an effective amount of an active agent,

or a pharmaceutically acceptable salt thereof, and a polymer to form an immediate-release compartment; combining an effective amount of an active agent, or a pharmaceutically acceptable salt thereof, and a combination of hydrophilic and hydrophobic polymers to form an extended-release compartment; and press coating the 5 extended-release compartment to substantially envelop the immediate-release compartment.

A preferred embodiment further includes the steps of combining an effective amount of an active agent, or a pharmaceutically acceptable salt thereof, and a polymer to form an instant-release compartment, and press coating the instant-release 10 compartment to substantially envelop the extended-release compartment.

In another preferred embodiment, the combining steps can be done by blending, wet granulation, fluid-bed granulation, or dry granulation according to methods recognized the art.

Other objects, features and advantages of the present invention will become 15 apparent from the following detailed description. The detailed description and the specific examples, however, indicate only preferred embodiments of the invention. Various changes and modifications within the spirit and scope of the invention will 20 become apparent to those skilled in the art from this detailed description.

20

Description of Drawings

Figure 1 is a schematic of a press coated, pulsatile drug delivery system of the present invention suitable for oral administration with an immediate-release compartment, which contains a compressed blend of an active agent and one or more 25 polymers, substantially enveloped by an extended-release compartment, which contains a compressed blend of the active agent and hydrophilic and hydrophobic polymers.

Figure 2 is a schematic of a press coated, pulsatile drug delivery system of the present invention suitable for oral administration with an immediate-release compartment, which contains a compressed blend of an active agent and one or more polymers, substantially enveloped by an extended-release compartment, which contains 5 a compressed blend of the active agent and hydrophilic and hydrophobic polymers, and substantially enveloped by an instant-release compartment.

Figure 3 is a graph showing the *in vitro* dissolution profile (% dissolved versus time) of isosorbide mononitrate extended release tablets, according to an embodiment of the present invention, in deionized water using a type 2 dissolution apparatus (paddle 10 method) at $37 \pm 0.5^\circ\text{C}$ at 75 rotations per minute (rpm). See U.S. Pharmacopeia XXII <711> Dissolution. The graph reflects the following data:

Time (minutes)	Mean Percent Dissolved	Standard deviation (n=12)
0	0	0
30	11.3	0.4
60	17.1	0.6
120	25.7	1.2
180	32.1	1.6
240	55.8	21.6
300	90.9	11.0
330	95.6	4.8
360	97.5	4.1
420	98.8	4.2
480	98.9	4.5
540	99.0	4.6
600	98.3	4.8

Figure 4 is a graph showing the *in vitro* dissolution profile (% dissolved versus 15 time) of isosorbide mononitrate extended release tablets, according to an embodiment of the present invention, in deionized water using USP paddle method at 75 rpm. The graph reflects the following data:

Time (minutes)	Percent Dissolved	Standard deviation
0	0	0
30	20.2	0.8
60	23.3	0.8
120	27.8	0.8
180	31.4	0.9
240	35.2	1.5
300	74.4	25.8
330	91.4	4.8
360	94.2	2.4
420	95.6	1.6
480	96.1	1.6
540	96.2	1.4

Detailed Description of Preferred Embodiments

In accordance with the present invention, the term "active agent" includes one or 5 more drugs, their pharmaceutically acceptable salts, pro-drug forms, metabolites, and derivatives.

Active agents include therapeutic or prophylactic compounds as described in the Physicians' Desk Reference, most preferably including (but not limited to) those prescribed for the prevention and/or treatment of angina and hypertension: diltiazem, 10 trapidil, urapidil, benzodarone, dipyridamole, isosorbide mononitrate, and lidoflazine; and those prescribed for the prevention and/or treatment of rheumatic diseases such as rheumatoid arthritis: non-steroidal antiinflammatory drugs (NSAIDs) and steroid antiinflammatory drugs such as diclofenac sodium, ibuprofen, ketoprofen, disflunisal, piroxicam, motrin, and naproxen, and combinations thereof.

15 The active agent of the present invention also preferably includes drugs that are subject to the first pass effect. Various examples of such drugs include (but are not limited to) acetaminophen, aldosterone, alprenolol, amitryptyline, aspirin, beclomethasone, dipropionate, bromocriptine, butorphanol tartrate, chlormethiazole, chlorpheniramine, chlorpromazine HCl, cimetidine, codeine, cortisone, cyclobenzamine

HCl, desmethylimipramine, dextropropoxyphene, dihydroergotamine, diltiazem HCl, dobutamine HCl, domperidone, dopamine HCl, doxepin HCl, epinephrine, ergoloid mesylates, ergotamine tartrate estradiol, ethinylestradiol, flunisolide, fluorouracil, flurazepam HCl, 5-fluoro-21-deoxyuridine, furosemide, glipizide, glyburide, glyceryl 5 trinitrate, guanethidine sulfate, hydralazine HCl, imipramine HCl, indoramin, isoetharine HCl, isoethrine mesylate, isoprenaline, isoproterenol sulfate, isosorbide dinitrate, levallorphan tartrate, levodopa, lidocaine HCl, lignocaine, lorcainide, meperidine HCl, 6-mercaptopurine, metaproterenol sulfate, methoxamine HCl, methylphenidate, methylpreonisolone, methyltestosterone mesylate, metoclopramide, metoprolol tartrate, 10 morphine sulfate, nalbuphine HCl, naloxone HCl, neostigmine, nifedipine, nitrendipine, nitroglycerin, norepinephrine bitartrate, norethindrone, nortriptylene HCl, oxprenolol, oxyphenbutazone, penicillamine, pentazocine HCl, pentazocine lactate, pentobarbital, petnidine, phenacetin, phentolamine HCl, phentolamine mesylate, phenylephrine HCl, phenylephrine bitartrate, phenytoin, pindolol, prazosin, prednisone, progesterone, 15 propoxyphene HCl, propoxyphene napsylate, propranolol HCl, quinidine, reserpine, ritodrine HCl, salicylamide, salbutamol, secobarbital, testosterone, terbutaline, timolol maleate, tolbutamide, and verapamil HCl.

In a preferred embodiment of the present invention, the active agent may include the drug, isosorbide-5-mononitrate, an organic nitrate, which is a vasodilator with effects 20 on both arteries and veins. The empirical formula is $C_6H_9NO_6$ and the molecular weight is 191.14. The chemical name for isosorbide mononitrate is 1,4:3,6-dianhydro-D-glucitol 5-nitrate.

Isosorbide mononitrate is the major active metabolite of isosorbide dinitrate and most of the clinical activity of the dinitrate can be attributable to the mononitrate. A 25 principal pharmacological action of isosorbide mononitrate is relaxation of vascular

smooth muscle and consequent dilatation of peripheral arteries and veins, especially the latter. Dilatation of the veins is known to promote peripheral pooling of blood and decrease venous return to the heart, thereby reducing left ventricular end-diastolic pressure and pulmonary capillary wedge pressure (preload). Arteriolar relaxation 5 reduces systemic vascular resistance, systolic arterial pressure, and mean arterial pressure (afterload). Dilation of the coronary arteries also occurs. The relative importance of preload reduction, afterload reduction, and coronary dilatation remains undefined. The mechanism by which isosorbide mononitrate relieves angina pectoris is not fully understood.

10 Isosorbide mononitrate is rapidly and completely absorbed from the gastrointestinal tract. In humans, isosorbide mononitrate is not subject to first pass metabolism in the liver. The overall elimination half-life of isosorbide mononitrate is about 6 hours. The rate of clearance is the same in healthy young adults, and in patients with various degrees of renal, hepatic, or cardiac dysfunction.

15 In accordance with the present invention, the term "polymer" includes single or multiple polymeric substances, which can swell, gel, degrade or erode on contact with an aqueous environment (e.g., water), such as one or more of alginic acid, carboxymethylcellulose calcium, carboxymethylcellulose sodium, colloidal silicon dioxide, croscarmellose sodium, crospovidone, guar gum, magnesium aluminum silicate, 20 methylcellulose, microcrystalline cellulose, polacrilin potassium, powdered cellulose, pregelatinized starch, sodium alginate, sodium starch glycolate, starch, ethylcellulose, gelatin, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polymethacrylates, povidone, pregelatinized starch, shellac, and zein, and combinations thereof.

The "hydrophilic polymers" of the present invention include one or more of carboxymethylcellulose, guar gum, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose, and povidone. The "hydrophobic polymers" of the present invention include one or more of carbomer, carnauba wax, 5 ethylcellulose, glyceryl palmitostearate, hydrogenated castor oil, hydrogenated vegetable oil type 1, microcrystalline wax, polacrilin potassium, polymethacrylates, and stearic acid.

Without further elaboration, it is believed that one skilled in the art, using the preceding description, can utilize the present invention to the fullest extent. The 10 following examples are illustrative only, and not limiting of the remainder of the disclosure in any way whatsoever.

Examples

Example 1

15 The method below was employed to obtain a press coated, pulsatile drug delivery system, the composition of which is set forth in the tables immediately following:

Immediate-Release Compartment. Isosorbide mononitrate was first mixed with silicon dioxide in a Patterson-Kelley V-blender for 10 minutes, then 20 microcrystalline cellulose and croscarmellulose sodium were added and blended for 10 more minutes. Finally, magnesium stearate was added to the blender and mix for another 10 minutes. The powder blend was then compressed using a Manesty Dry-cota with 0.2031" in diameter, round, flat-face punch and die set. The hardness of the tablets were maintained at 4 ± 2 kp.

25 Immediate-Release Compartment Plus Extended-Release Compartment

Isosorbide mononitrate was first mixed with silicon dioxide in a Patterson-Kelley V-

blender for 10 minutes, then hydroxypropyl methylcellulose 2208 and microcrystalline cellulose were added and blended for 10 more minutes. Finally, hydrogenated vegetable oil and magnesium stearate were added to the blender and mix for another 10 minutes. The core tablets were press-coated using the Manesty Dry-cota with 0.3600" in 5 diameter, round, shallow concave punch and die set. The hardness of the tablets were maintained at 12 ± 4 kp.

Example 2

Immediate-Release Compartment Plus Extended-Release Compartment Plus

Instant-Release Compartment The method of manufacture for the extended-release 10 tablets is the same as described in Example 1. The application of the instant-release compartment was done by charging the extended-release tablets into a perforated pan coater or a fluidized particle coater and coated with a solution consist of isosorbide-5-mononitrate 80% w/ lactose and hydroxypropyl methylcellulose type 2910. The instant release coating may also be applied using the press-coating process described in 15 Example 1 above with a blend consisting of isosorbide-5-mononitrate 80% w/ lactose and hydroxypropyl methylcellulose type 2910.

In addition, the formulation of respective release compartments can occur by appropriate granulation methods. In wet granulation, solutions of the binding agent (polymer) are added with stirring to the mixed powders. The powder mass is wetted 20 with the binding solution until the mass has the consistency of damp snow or brown sugar. The wet granulated material is forced through a sieving device. Moist material from the milling step is dried by placing it in a temperature controlled container. After drying, the granulated material is reduced in particle size by passing through a sieving device. Lubricant is added, and the final blend is then compressed.

In fluid-bed granulation, particles of inert material and/or active agent are suspended in a vertical column with a rising air stream. While the particles are suspended, the common granulating materials in solution are sprayed into the column. There is a gradual particle buildup under a controlled set of conditions resulting in tablet 5 granulation. Following drying and the addition of lubricant, the granulated material is ready for compression.

In dry-granulation, the active agent, diluent, and lubricant are blended and compressed into large tablets. The compressed large tablets are comminuted through the desirable mesh screen by sieving equipment. Some more lubricant is added to the 10 granulated material and blended gently. The material is then compressed into tablets.

TABLE 1

	Quantity/Tablet	
	Example #1	Example #2
Immediate-Release (IR) Compartment	RT-010 (press-coated w/o instant-release coating)	RT-011 (press coated w/ instant-release coating)
Isosorbide-5-mononitrate 80% w/ lactose	50.0 mg	50.0 mg
Croscarmellose sodium	1.6 mg	1.6 mg
Microcrystalline cellulose	26.8 mg	26.8 mg
Colloidal silicon dioxide	0.8 mg	0.8 mg
Magnesium stearate	0.8 mg	0.8 mg
Total:	80.0 mg	80.0 mg
IR Compartment Plus Extended-Release (ER) Compartment		
IR Compartment	80.0 mg	80.0 mg
Isosorbide-5-mononitrate 80% w/ lactose	37.5 mg	18.8 mg
Hydroxypropyl methylcellulose type 2208	61.6 mg	61.6 mg
Microcrystalline cellulose	70.3 mg	89.0 mg
Hydrogenated vegetable oil type 1	46.2 mg	46.2 mg
Colloidal silicon dioxide	2.2 mg	2.2 mg
Magnesium stearate	2.2 mg	2.2 mg
Total:	300.0 mg	300.00 mg
IR Compartment Plus ER Compartment Plus Instant-Release Compartment		
IR Compartment Plus ER Compartment		300.0 mg
Isosorbide-5-mononitrate 80% w/ lactose		18.7 mg
Hydroxypropyl methylcellulose type 2910		1.9 mg
Total:		320.6 mg

TABLE 2

EXCIPIENT RANGE			
Immediate-Release Compartment	Quantity/tablet Example #1 RT-010 (press coated w/o instant-release coating)	Percent	Range
Isosorbide-5-mononitrate 80% w/ lactose	50.0 mg	62.5%	
Croscarmellose sodium	1.6 mg	2.0%	0.5 -10.0%
Microcrystalline cellulose	26.8 mg	33.5%	18.0-36.0%
Colloidal silicon dioxide	0.8 mg	1.0%	0.5-2.0%
Magnesium stearate	0.8 mg	1.0%	0.5-2.0%
Total:	80.0 mg		
Extended-Release Compartment			
Isosorbide-5-mononitrate 80% w/ lactose	37.5 mg	17.0%	
Hydroxypropyl methylcellulose type 2208	61.6 mg	28.0%	15.0-40.0%
Microcrystalline cellulose	70.3 mg	32.0%	8.0-57.0%
Hydrogenated vegetable oil type 1	46.2 mg	21.0%	10.0-30.0%
Colloidal silicon dioxide	2.2 mg	1.0%	0.5-2.0%
Magnesium stearate	2.2 mg	1.0%	0.5-2.0%
Total:	220.0 mg		

The invention has been disclosed broadly and illustrated in reference to representative embodiments described above. Those skilled in the art will recognize that 5 various modifications can be made to the present invention without departing from the spirit and scope thereof.

What is claimed is:

1. A drug delivery system suitable for oral administration comprising:
 - (a) an immediate-release compartment comprising a compressed blend of an effective amount of an active agent, or a pharmaceutically acceptable salt thereof, and a polymer; and
 - (b) an extended-release compartment, which substantially envelops said immediate-release compartment, comprising a combination of a hydrophilic and hydrophobic polymer.
2. The drug delivery system of claim 1, wherein said extended-release compartment further comprises an effective amount of an active agent, or a pharmaceutically acceptable salt thereof, in a compressed blend with said combination of a hydrophilic and hydrophobic polymer.
3. The drug delivery system of claim 1, which further comprises an inert core, which is substantially enveloped by said immediate-release compartment.
4. The drug delivery system of claim 1, which further comprises an instant-release compartment, which substantially envelops said extended-release compartment, comprising a compressed blend of an effective amount of said active agent, or a pharmaceutically acceptable salt thereof, and a polymer.
5. The drug delivery system of claim 2, which further comprises an instant-release compartment, which substantially envelops said extended-release compartment, comprising a compressed blend of an effective amount of said active agent, or a pharmaceutically acceptable salt thereof, and a polymer.
6. The drug delivery system of claim 1, wherein said active agent is a drug.

7. The drug delivery system of claim 6, wherein said drug is a therapeutic drug.

8. The drug delivery system of claim 6, wherein said drug is a prophylactic drug.

9. The drug delivery system of claim 6, wherein said drug is selected from the group consisting of diltiazem, trapidil, urapidil, benziodarone, dipyridamole, isosorbide mononitrate, and lidoflazine.

10. The drug delivery system of claim 6, wherein said drug is selected from the group consisting of non-steroidal antiinflammatory drugs (NSAIDs) and steroidal antiinflammatory drugs.

11. The drug delivery system of claim 10, wherein said steroidal antiinflammatory drug is selected from the group consisting of diclofenac sodium, ibuprofen, ketoprofen, diflunisal, piroxicam, motrin, and naproxen.

12. The drug delivery system of claim 6, wherein said drug is selected from the group consisting of acetaminophen, aldosterone, alprenolol, amitryptyline, aspirin, beclomethasone, dipropionate, bromocriptine, butorphanol tartrate, chlormethiazole, chlorpheniramine, chlorpromazine HCl, cimetidine, codeine, cortisone, cyclobenzamine HCl, desmethylimipramine, dextropropoxyphene, dihydroergotamine, diltiazem HCl, dobutamine HCl, domperidone, dopamine HCl, doxepin HCl, epinephrine, ergoloid mesylates, ergotamine tartrate estradiol, ethinylestradiol, flunisolide, fluorouracil, flurazepam HCl, 5-fluoro-21-deoxyuridine, furosemide, glipizide, glyburide, glyceryl trinitrate, guanethidine sulfate, hydralazine HCl, imipramine HCl, indoramin, isoetharine HCl, isoethrine mesylate, isoprenaline, isoproterenol sulfate, isosorbide dinitrate, levallorphan tartrate, levodopa, lidocaine HCl, lignocaine, lorcainide, meperidine HCl, 6-mercaptopurine, metaproterenol

sulfate, methoxamine HCl, methylphenidate, methylprednisolone, methyltestosterone mesylate, metoclopramide, metoprolol tartrate, morphine sulfate, nalbuphine HCl, naloxone HCl, neostigmine, nifedipine, nitrendipine, nitroglycerin, norepinephrine bitartrate, norethindrone, nortriptyline HCl, oxprenolol, oxyphenbutazone, penicillamine, pentazocine HCl, pentazocine lactate, pentobarbital, petnidine, phenacetin, phentolamine HCl, phentolamine mesylate, phenylephrine HCl, phenylephrine bitartrate, phenytoin, pindolol, prazosin, prednisone, progesterone, propoxyphene HCl, propoxyphene napsylate, propranolol HCl, quinidine, reserpine, ritodrine HCl, salicylamide, salbutamol, secobarbital, testosterone, terbutaline, timolol maleate, tolbutamide, and verapamil HCl.

13. The drug delivery system of claim 6, wherein said active agent is isosorbide-5-mononitrate.

14. The drug delivery system of claim 2, wherein said active agent exhibits the following *in vitro* dissolution profile when measured in a type 2 dissolution apparatus (paddle) according to U.S. Pharmacopeia XXII at 37°C in deionized water at 75 rotations per minute:

(c) from about 0% to about 90% of said active agent is released between 1 hour and 16 hours of measurement in said apparatus; and

(d) from about 0% to about 100% of said active agent is released between 1.5 hours and 28 hours after measurement in said apparatus.

15. The drug delivery system of claim 14, wherein said active agent exhibits the following *in vitro* dissolution profile when measured in a type 2 dissolution apparatus (paddle) according to U.S. Pharmacopeia XXII at 37°C in deionized water at 75 rotations per minute:

(c) from about 10% to about 75% of said active agent is released

between 1 hour and 5 hours of measurement in said apparatus; and

(d) no less than about 90% of said active agent is released after 6

hours of measurement in said apparatus.

16. The drug delivery system of claim 15, wherein said active agent is

isosorbide-5-mononitrate.

17. The drug delivery system of claim 5, wherein said active agent exhibits

the following *in vitro* dissolution profile when measured in a type 2 dissolution

apparatus (paddle) according to U.S. Pharmacopeia XXII at 37°C in deionized water

at 75 rotations per minute:

(d) from about 0% to about 50% of said active agent is released after 1

hour of measurement in said apparatus;

(e) from about 0% to about 90% of said active agent is released

between 1 hour and 16 hours after measurement in said apparatus; and

(f) from about 0% to about 100% of said active agent is released

between 1.5 hours and 28 hours after measurement in said apparatus.

18. The drug delivery system of claim 17, wherein said active agent

exhibits the following *in vitro* dissolution profile when measured in a type 2

dissolution apparatus (paddle) according to U.S. Pharmacopeia XXII at 37°C in

deionized water at 75 rotations per minute:

(g) from about 0% to about 35% of said active agent is released after 1

hour of measurement in said apparatus;

(h) from about 10% to about 90% of said active agent is released

between 1 hour and 5 hours after measurement in said apparatus; and

(i) no less than 90% of said active agent is released after 6 hours of measurement in said apparatus.

19. The drug delivery system of claim 17, wherein said active agent is isosorbide-5-mononitrate.

20. The drug delivery system of claim 1, wherein said polymer is selected from the group consisting of alginic acid, carboxymethylcellulose calcium, carboxymethylcellulose sodium, colloidal silicon dioxide, croscarmellose sodium, crospovidone, guar gum, magnesium aluminum silicate, magnesium stearate, methylcellulose, microcrystalline cellulose, polacrilin potassium, powdered cellulose, pregelatinized starch, sodium alginate, sodium starch glycolate, starch, ethylcellulose, gelatin, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polymethacrylates, povidone, shellac, and zein.

21. The drug delivery system of claim 20, wherein said polymer is selected from the group consisting of colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, microcrystalline cellulose, and hydroxypropyl methylcellulose.

22. The drug delivery system of claim 1, wherein said hydrophilic polymer is selected from the group consisting of carboxymethylcellulose, guar gum, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose, and povidone.

23. The drug delivery system of claim 22, wherein said hydrophilic polymer is hydroxypropyl methylcellulose.

24. The drug delivery system of claim 1, wherein said hydrophobic polymer is selected from the group consisting of carbomer, carnauba wax, ethylcellulose, glyceryl palmitostearate, hydrogenated castor oil, hydrogenated

vegetable oil type 1, microcrystalline wax, polacrilin potassium, polymethacrylates, and stearic acid.

25. The drug delivery system of claim 24, wherein said hydrophobic polymer is hydrogenated vegetable oil type 1.

26. A method for preparing a drug delivery system suitable for oral administration comprising the steps of:

(a) combining an effective amount of an active agent, or a pharmaceutically acceptable salt thereof, and a polymer to form an immediate-release compartment;

(b) combining an effective amount of an active agent, or a pharmaceutically acceptable salt thereof, and a hydrophilic and a hydrophobic polymer to form an extended-release compartment; and

(c) press coating said extended-release compartment to substantially envelop said immediate-release compartment.

27. The method of claim 26, which further comprises:

(d) combining an effective amount of an active agent, or a pharmaceutically acceptable salt thereof, and a polymer to form an instant-release compartment; and

(e) press coating said instant-release compartment to substantially envelop said extended-release compartment.

28. The method of claim 26, wherein said combining is selected from the group consisting of blending, perforated pan coating, fluidized particle coating, wet granulation, fluid-bed granulation, and dry granulation.

29. The method of claim 26, wherein said active agent is a drug.

30. The method of claim 29, wherein said drug is a therapeutic drug.

31. The method of claim 29, wherein said drug is a prophylactic drug.
32. The method of claim 29, wherein said drug is selected from the group consisting of diltiazem, trapidil, urapidil, benziodarone, dipyridamole, isosorbide mononitrate, and lidoflazine.
33. The method of claim 29, wherein said drug is selected from the group consisting of non-steroidal antiinflammatory drugs (NSAIDs) and steroidal antiinflammatory drugs.
34. The method of claim 33, wherein said steroidal antiinflammatory drug is selected from the group consisting of diclofenac sodium, ibuprofen, ketoprofen, diflunisal, piroxicam, motrin, and naproxen.
35. The method of claim 29, wherein said drug is selected from the group consisting of acetaminophen, aldosterone, alprenolol, amitryptyline, aspirin, beclomethasone, dipropionate, bromocriptine, butorphanol tartrate, chlormethiazole, chlorpheniramine, chlorpromazine HCl, cimetidine, codeine, cortisone, cyclobenzamine HCl, desmethylimipramine, dextropropoxyphene, dihydroergotamine, diltiazem HCl, dobutamine HCl, domperidone, dopamine HCl, doxepin HCl, epinephrine, ergoloid mesylates, ergotamine tartrate estradiol, ethinylestradiol, flunisolide, fluorouracil, flurazepam HCl, 5-fluoro-21-deoxyuridine, furosemide, glipizide, glyburide, glyceryl trinitrate, guanethidine sulfate, hydralazine HCl, imipramine HCl, indoramin, isoetharine HCl, isoethrine mesylate, isoprenaline, isoproterenol sulfate, isosorbide dinitrate, levallorphan tartrate, levodopa, lidocaine HCl, lignocaine, lorcainide, meperidine HCl, 6-mercaptopurine, metaproterenol sulfate, methoxamine HCl, methylphenidate, methylprednisolone, methyltestosterone mesylate, metoclopramide, metoprolol tartrate, morphine sulfate, nalbuphine HCl, naloxone HCl, neostigmine, nifedipine, nitrendipine, nitroglycerin, norepinephrine

bitartrate, norethindrone, nortriptylene HCl, oxprenolol, oxyphenbutazone, penicillamine, pentazocine HCl, pentazocine lactate, pentobarbital, petnidine, phenacetin, phentolamine HCl, phentolamine mesylate, phenylephrine HCl, phenylephrine bitartrate, phenytoin, pindolol, prazosin, prednisone, progesterone, propoxyphene HCl, propoxyphene napsylate, propranolol HCl, quinidine, reserpine, ritodrine HCl, salicylamide, salbutamol, secobarbital, testosterone, terbutaline, timolol maleate, tolbutamide, and verapamil HCl.

36. The method of claim 26, wherein said active agent is isosorbide-5-mononitrate.

37. The method of claim 26, wherein said polymer is selected from the group consisting of alginic acid, carboxymethylcellulose calcium, carboxymethylcellulose sodium, colloidal silicon dioxide, croscarmellose sodium, crospovidone, guar gum, magnesium aluminum silicate, magnesium stearate, methylcellulose, microcrystalline cellulose, polacrilin potassium, powdered cellulose, pregelatinized starch, sodium alginate, sodium starch glycolate, starch, ethylcellulose, gelatin, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polymethacrylates, povidone, shellac, and zein.

38. The method of claim 37, wherein said polymer is selected from the group consisting of colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, microcrystalline cellulose, and hydroxypropyl methylcellulose.

39. The method of claim 26, wherein said hydrophilic polymer is selected from the group consisting of carboxymethylcellulose, guar gum, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose, and povidone.

40. The method of claim 39, wherein said hydrophilic polymer is hydroxypropyl methylcellulose.

41. The method of claim 26, wherein said hydrophobic polymer is selected from the group consisting of carbomer, carnauba wax, ethylcellulose, glyceryl palmitostearate, hydrogenated castor oil, hydrogenated vegetable oil type 1, microcrystalline wax, polacrilin potassium, polymethacrylates, and stearic acid.

42. The method of claim 41, wherein said hydrophobic polymer is hydrogenated vegetable oil type 1.

1/4

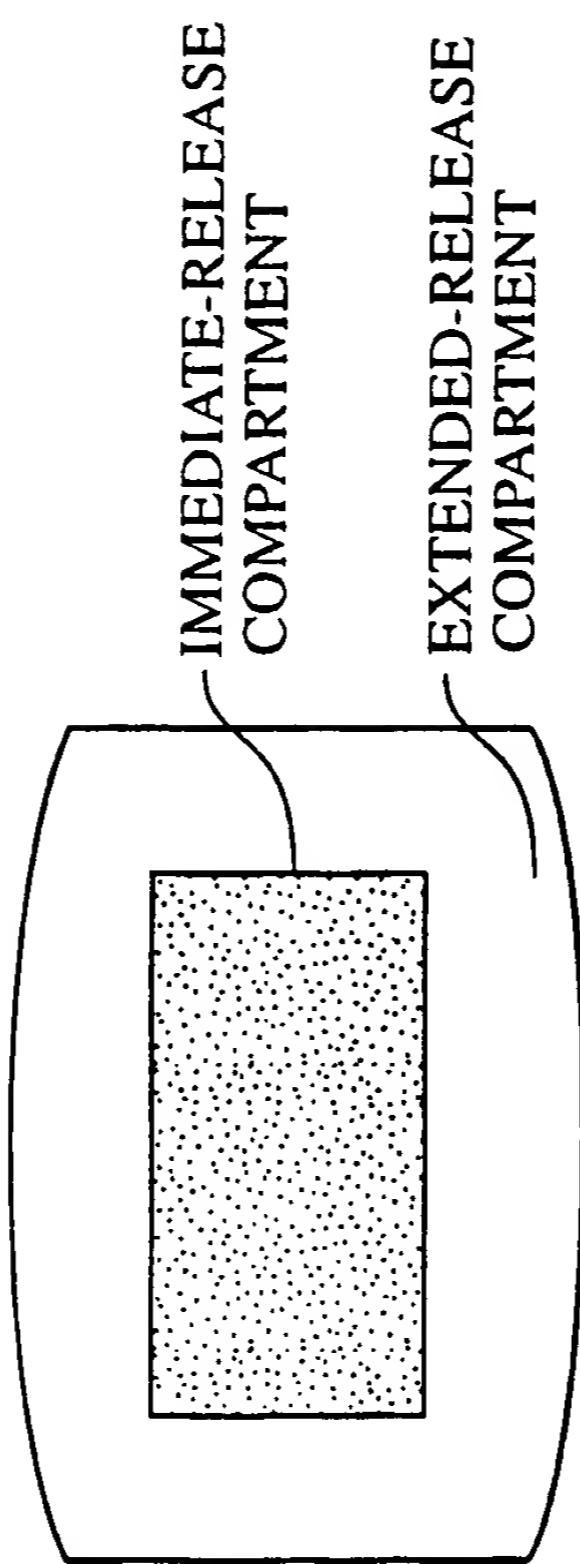


FIG. 1

2/4

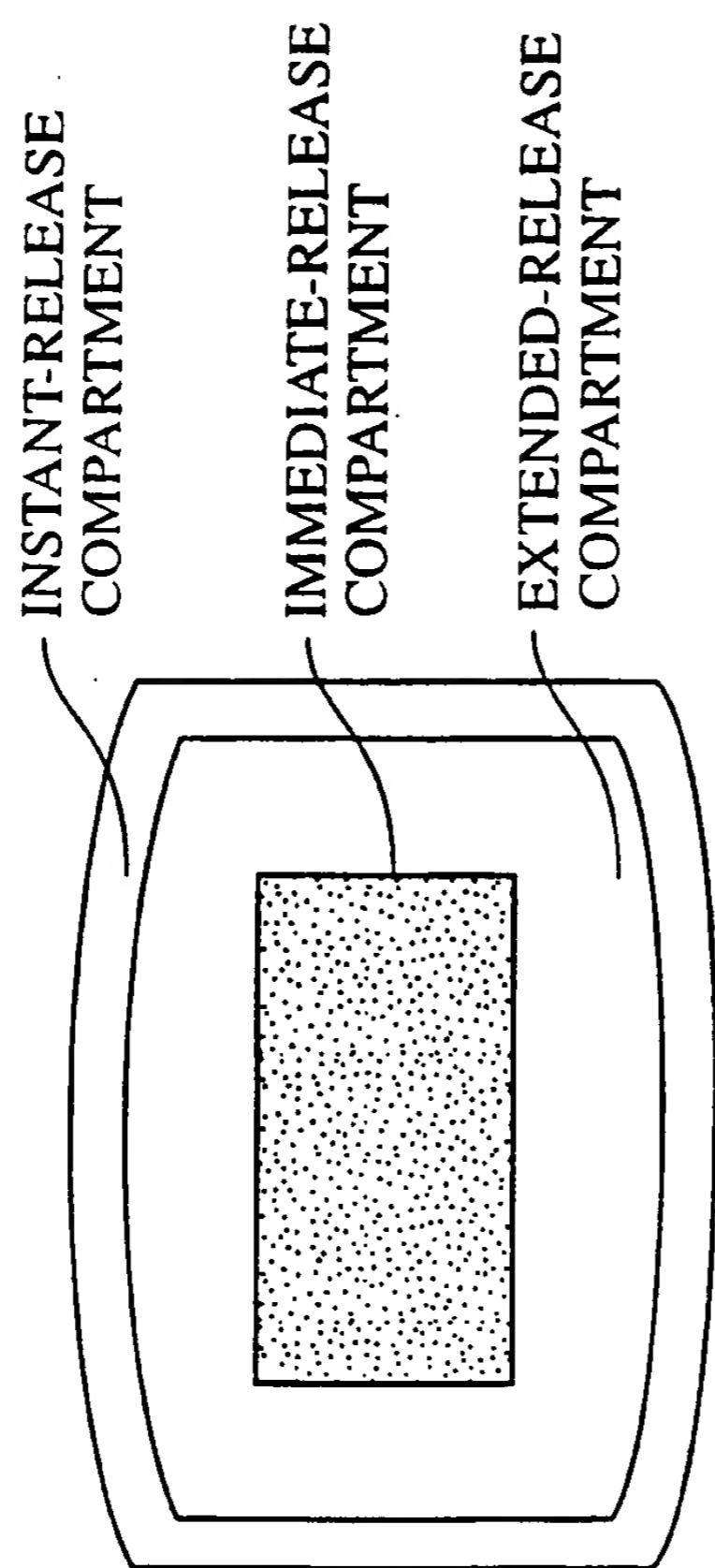


FIG. 2

3/4

IN-VITRO DISSOLUTION OF ISOSORBIDE MONONITRATE
EXTENDED RELEASE TABLETS LOT #RT-010, 70 mg IN DI WATER

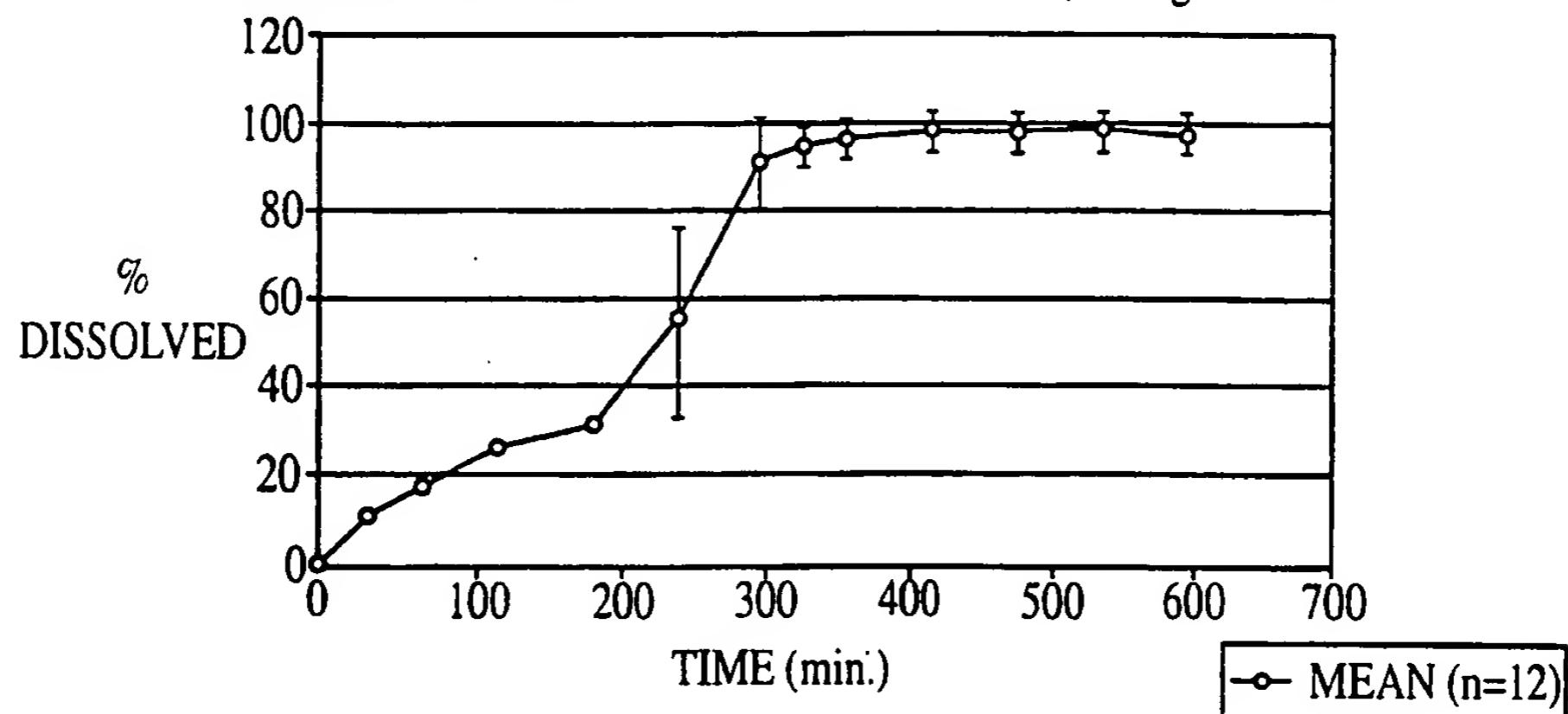


FIG. 3

4/4

IN-VITRO DISSOLUTION OF ISOSORBIDE MONONITRATE
EXTENDED RELEASE TABLETS LOT #RT-011, 70 mg IN DI WATER

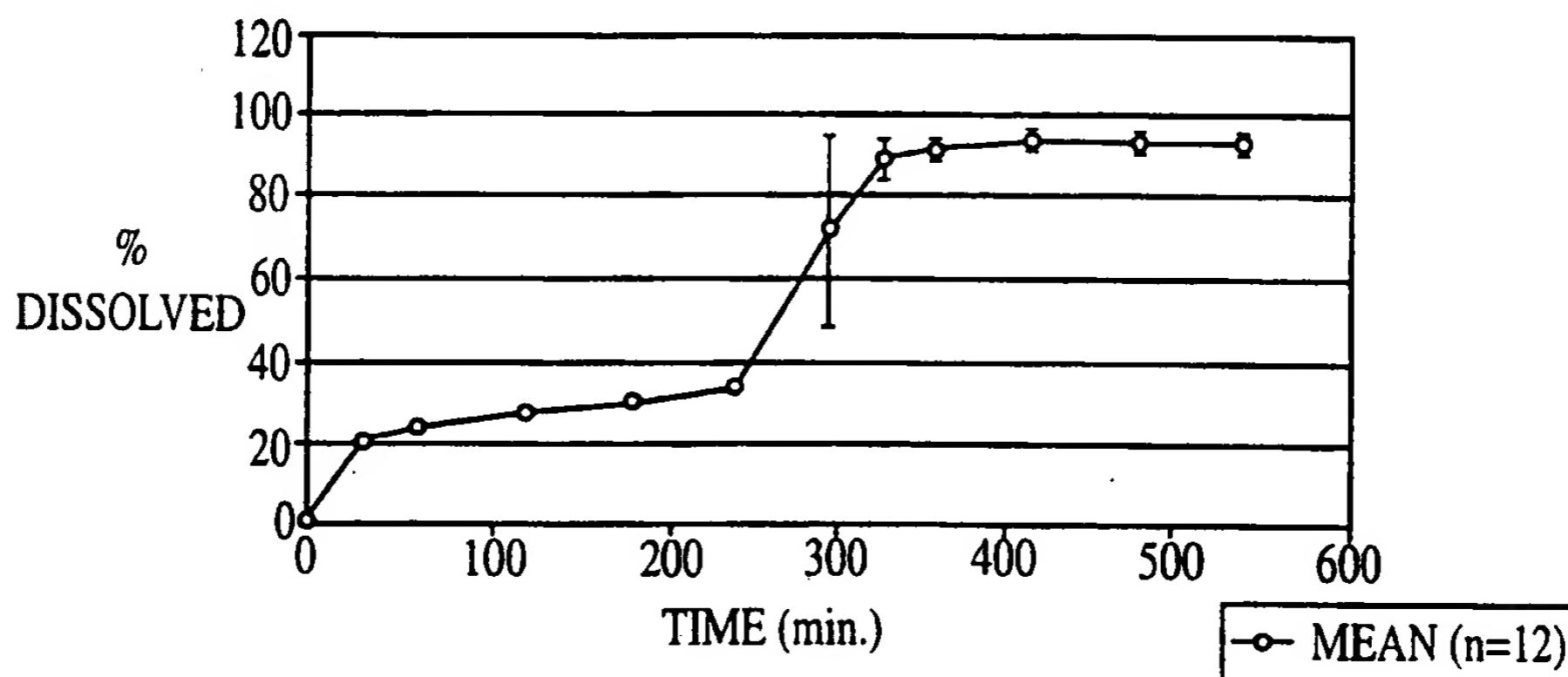


FIG. 4

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/06987

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : A61K 9/22
US CL : 424/468

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/468

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
NONEElectronic data base consulted during the international search (name of data base and, where practicable, search terms used)
APS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,374,759 A (IMPERANTE et al) 20 DECEMBER 1994, see entire document.	1-42
Y	US 5,334,372 A (KAWAMATA et al) 02 August 1994, see entire document.	1-42
Y	CHEMICAL ABSTRACTS, Vol. 67, 1967, Accession No. 78733, FOLTZ et al., 'Reactants of Labile Trimethylsilyl derivatives with Fluorocarbons in a gas chromatograph-mass spectrometer system. Anal. Chem. Abstract, 1967, 39(11), 1338-1339, See entire document.	1-42

Further documents are listed in the continuation of Box C.

See patent family annex.

• Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
• "A" document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
• "E" earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
• "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"A"	document member of the same patent family
• "O" document referring to an oral disclosure, use, exhibition or other means		
• "P" document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

26 MAY 1999

Date of mailing of the international search report

30 AUG 1999

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

D. Lawrence Fer
PETER KULKOSKY

Telephone No. (703) 308-1235